Review article

DUPUYTREN'S DISEASE

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The current state of knowledge of Dupuytren's disease is rather like a complex jigsaw puzzle, many pieces of which have been gathered in many countries, but exactly where each fits into the finished puzzle is not clear. Some may not even belong to this particular puzzle. At present there are some theories and some science, with some correlation, but there is still some way to go.

The history of Dupuytren's disease

As recently as 1962 it was suggested that the condition originated in the Nordic races[1] and it became known as the Viking disease.[2] Although it most commonly affects fair-skinned individuals with blond hair there is little evidence to support its Nordic origin.[3] The disease is now so widespread that proof of its origin from any one race would be an almost impossible task.[3] The earliest record of the disease has come from a study of the Icelandic sagas in which during the 12th and 13th centuries, four miracle cures of putative Dupuytren's disease were effected by priests in Orkney and Iceland.[4]

There is little concerning the abnormality in the literature of the 16th century, possibly due to the short life expectancy during those times, although it was known to be prevalent in the Western Isles of Scotland where it came to be known as the Curse of the MacCrimmons. The MacCrimmons were musicians and pipers to the chieftains of the Clan MacLeod of Skye. The contracture made the playing of the bagpipes impossible. This was a considerable social impediment since good pipers stood second only to the chieftains in the society of 16th century Skye.[5]

The first written description was by Platter of Basel, Switzerland in 1614. He noted how, in the hands of a master

mason, the tendons of the ring and little fingers ceased to function. The tendons contracted "and in doing so were loosed from the bonds by which they are held and became raised up, as two cords forming a ridge under the skin".[6] This anatomical error is somewhat mystifying since it is known that Platter had a good knowledge of anatomy, and it suggests that he had not dissected an affected hand. His error has been perpetuated to this day because patients are still sent along to hand clinics with a note from their doctor referring to "contracted flexor tendons".

Pre-eminent in the late 18th and early 19th centuries were the Hunter brothers of whom John is considered to be the father of British surgery. It was one of John Hunter's pupils, Henry Cline (1759-1826), who first dissected a hand with Dupuytren's disease. In 1777, the year of Dupuytren's birth, he dissected two cadaver hands with contractures of the fingers and proposed palmar fasciotomy as a cure.[7] He taught his observations to surgical apprentices at St Thomas' Hospital in London, one of whom was the wayward nephew of William Cooper, then the senior surgeon at Guy's Hospital. Young Astley Cooper served an apprenticeship of five years and was then invited by Cline to share his lectures. Cooper wrote of Dupuytren's disease in 1822: "...when the aponeurosis is the cause of the contraction, and the contracted band is narrow, it may with advantage be divided with a pointed bistory...".[8] He was to be misquoted repeatedly in the French literature, first by Dupuytren[5] who declared that Cooper had stated that the disease was incurable. "Asthley (sic) Cooper...le célèbre chirurgien anglais lui répondit que la maladie était incurable".[9]

Much more was written in the French literature about the disease of M. le Baron Dupuytren over the ensuing years. From Paris the fashion for the surgical treatment of what had then become known as Dupuytren's disease had spread across Europe and to England. This would have brought it to the awareness of a new generation of surgeons, the work of Cline and Cooper having been largely forgotten. It must be accepted that Dupuytren did much to further the understanding of the condition which now bears his name.

The biology of Dupuytren's disease

Myofibroblasts. These share morphological features with fibroblasts and smooth muscle cells.[10] In particular, like the

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fibroblast, the myofibroblast has bundles of actin microfilaments (stress fibres) arranged parallel to the long axis of the cell. It is similar to the smooth-muscle cell in that it has a Golgi apparatus and a dilated rough endoplasmic reticulum.[11] Filaments of fibronectin, a glycoprotein, are arranged into extracellular bundles at the surface of the myofibroblast. The actin microfilaments appear to become continuous at the cell surface with fibres of fibronectin at special attachment sites called the fibronexus, and are present at the surfaces of myofibroblasts in Dupuytren's disease.[12,13] The intracellular actin is linked by the integrin transmembrane glycoprotein, α5β1, with the extracellular fibronectin.[14]

Actin activity. There are six different isoforms of actin.[15] The expression of α-smooth-muscle actin increases during wound healing and disappears during scar formation,[16] and appears to be transient in Dupuytren's disease.[11] It corresponds to the increased generation of contractile force.[17,18] It has been suggested that it is the interaction of the actin in close association with myosin in the fibroblasts which is responsible for the development of the contractile force.[19,20] This phenomenon has been demonstrated in granulation tissue[21] but not as yet in Dupuytren's tissue.

Origin of myofibroblasts. Fibroblasts can be induced to express α-smooth-muscle actin by treatment with transforming growth factor-β1 (TGF-β1). This was demonstrated by Vaughan and Tomasek[22] who described the promotion of the development of fibrils of fibronectin and the associated fibronexus by the interaction between fibroblasts and TGF-β1. Their findings suggest that fibroblasts can be induced to transform into myofibroblasts by stimulation with TGF-β1. The latter has been isolated from Dupuytren's nodules where it could, conceivably, stimulate the formation of myofibroblasts.

Some myofibroblasts arise from vascular smooth-muscle cells. The detection of desmin, an intermediate filament protein found in smooth-muscle cells, in myofibroblasts from Dupuytren's tissues[23,24] suggests that some myofibroblasts arise from vascular smooth-muscle cells, but most are derived from fibroblasts in the palmar aponeurosis.[11]

Myofibroblast control factors. Three distinct histological phases have been described by Luck.[25] These are:

Proliferative. There is local fibroplasia in the fascia and the development of a nodular lesion with a proliferation of myofibroblasts which express α-smooth muscle actin.[23,24]

Involutional. The cells within the nodule realign themselves with the lines of stress in the tissues during which the same fibroblasts are present.

Residual. This corresponds to the disappearance of the nodule leaving relatively acellular, scar-like tissue and the absence of myofibroblasts.

The appearance and disappearance of myofibroblasts in Dupuytren's tissue are similar to those observed in other tissues in which fibroblasts are present, such as granulation tissue[16] and their control is also considered to be similar to that in granulation tissue. The actual processes of control in both are still being investigated. Two control factors have been postulated, namely, mechanical stress in the tissue[11,26] and TGF-β1.[11]

Interleukin-1, basic fibroblast growth factor and transforming growth factor-β stimulate the growth of fibroblasts. TGF-β1 also enhances the production of collagen and other extracellular matrix proteins[27] and may be relevant in the development of Dupuytren's disease. It is a multifunctional cytokine which plays a central role in stimulating the proliferation of fibroblasts and the deposition of extracellular matrix during wound healing. The effect of TGF-β on the proliferation of myofibroblasts has been studied using cultures from Dupuytren's nodules in the proliferative or involutional stage. The results from these cell cultures indicate that when compared with control myofibroblasts, the application of TGF-β1, TGF-β2 and TGF-β1+TGFβ2 had significant effects on the proliferation of myofibroblasts, especially at higher plating densities. TGF-β2, however, had the most significant proliferative effect.[28]

A number of other chemical mediators have been isolated from Dupuytren's tissue in vitro, but their relevance in the control and the progression of the disease is, as yet, uncertain. Magro et al[29] have suggested that the α5β1 integrin/fibronectin complex may be involved in regulating the interactions between myofibroblasts and the extracellular matrix. They have also suggested that the restricted co-expression of transforming growth factor-a (TGF-α) and epidermal growth factor-receptor (EGF-R) to myofibroblasts, the proliferating cellular component of nodules, suggests that an autocrine and/or juxtracrine growth stimulation by TGF-α via EGF-R may be involved in the pathogenesis of palmar fibromatosis.[30]

Control of myofibroblast contraction. The contraction of myofibroblasts has been found, in vitro, to depend on the presence of specific agonists. Lysophosphatidic acid (LPA), a phospholipid, has been shown to be a potent agonist which stimulates the contraction of myofibroblasts from Dupuytren's tissue.[31] Like prostaglandins, LPA can be released by cells into the extracellular milieu after stimulation by growth factor.[11] This phenomenon has yet to be demonstrated in Dupuytren's disease.

Other agonists include prostaglandins. Early investigations to determine if the vasoactive prostaglandins, $PGE_{2\alpha}$, and $PGF_{2\alpha}$, were identifiable in association with nodular myofibroblasts of patients with Dupuytren's disease found a significant increase in both prostaglandins, especially $PGF_{2\alpha}$, in the palmar fascia, when compared with control fascia. It was thought that these endogenous prostaglandins may influence the contractile behaviour of myofibroblasts in the condition.[32] They have been shown to promote force generation of fibroblasts. In their study, Hurst, Badalamente and Makowski[33] demonstrated the ability of prostaglandin $PGF_{2\alpha}$ to induce significant contraction of myofibroblasts. The contractile/relaxation responses of control fibroblasts to these prostaglandins were minimal. These authors have found that, in vitro, LPA is 1000 times stronger than $PGF_{2\alpha}$.

Manipulation of the controls. The work on interferon by Pittet et al[34] has shown that interferon-γ, from T-helper lymphocytes, has a number of effects on the function of fibroblasts and myofibroblasts in Dupuytren's disease. They found that it decreased the symptoms and the size of the lesions of both hypertrophic scars and Dupuytren's nodules. In hypertrophic scars, examination by immunofluorescence showed that expression of α-smooth-muscle was also decreased in myofibroblasts.[34] This may represent a way forward in the development of the non-surgical management of Dupuytren's disease.

Collagen types in Dupuytren's disease. In the normal palmar aponeurosis, type-I collagen predominates although type-III collagen has been found to be present in small quantities.[35] There have been a number of studies which have reported an increase in the ratio of type-I to type-III collagen in Dupuytren's disease.[36-43] These changes are similar to those found in hypertrophic scars and granulation tissue.[43] Apart from the changes to the biochemical constitution of type-III collagen, Brickley-Parsons et al[44] identified an increased total number of reducible cross-links between collagen chains. In another study of the collagen components in Dupuytren's tissue, Melling et al[45] found that the relative content of type-III collagen increased with increasing tissue involvement. They have also reported the presence of increased cross-linking between chains of type-III collagen in the palmar fascia of diabetics but decreased linking in similar tissue from patients with Dupuytren's disease.[46]

Magro et al[47] examined Dupuytren's tissue from 30 patients and, by an immunohistochemical study of the extracellular matrix (ECM), showed that collagen types IV and VI, laminin and fibronectin were strongly expressed and restricted to cellular areas of the involutional and residual phases. They suggested that interactions between myofibroblasts and the surrounding ECM glycoproteins may be involved in the pathophysiology of palmar fibromatosis.

Oxygen free radicals. At the cellular level, the controlling factors of Dupuytren's disease are most likely to be chemical.[48] All of the vascular, morphological and lipid studies are consistent with localised microvascular ischaemia in the palmar fascia.[49-57] During the metabolism of adenosine triphosphate (ATP), part of which is mediated by alcohol, xanthine oxidase catalyses the oxidation of hypoxanthine to xanthine and uric acid with the release of superoxide free radicals and hydroxyl radicals.[48] A six-fold increase in the concentration of hypoxanthine in Dupuytren's tissue and in the activity of xanthine oxidase have been demonstrated[58] and these have a stimulatory effect on the proliferation of fibroblasts.[56] Murrell et al[55] have also shown that agents which inhibit the formation of prostaglandin inhibited the release of free radicals and the proliferation of fibroblasts in vitro and have suggested that the same may be true in vivo.[48]

Autoimmune mechanisms. Previous reports have indicated that inflammatory mechanisms may be involved in the pathogenesis of Dupuytren's disease and it has even been suggested that this condition is a T-cell-mediated autoimmune phenomenon. Gudmundsson et al[59] investigated subsets of peripheral blood lymphocytes from 21 patients and compared them with those of ten healthy blood donors and found that the Dupuytren patients had an increase in DR+ T-cells when compared with the control group. They considered that these findings support previous suggestions that immunological mechanisms, involving activated T-cells and probably also B-cells, are involved in the pathogenesis of Dupuytren's disease.

Autoantibodies of connective tissue have also been implicated. In a study by Neumuller, Menzel and Millesi[60] 46 patients with Dupuytren's disease and 55 control subjects were HLA-typed for class-I and HLA-DR class-II antigens and were also investigated for the presence of autoantibodies against elastin (ELAB) and collagen types I to IV. A significant association was found between the affected patients and HLA-DR3 and autoantibodies to types I to IV. The authors suggested that the remodelling processes during the course of fibrosis may be responsible for this formation of autoantibodies. Pereira et al[61] have also reported an increase in the prevalence of antibody to denatured type-II collagen but no increase in HLA-DR4 when compared with a control group.

Inflammatory influences. A number of authors have reported the presence of inflammatory cells in biopsied Dupuytren's tissue. The nodules contain inflammatory cells, mainly lymphocytes and macrophages. These express a common integrin known as VLA4. The corresponding binding ligands to VLA4 are vascular cell adhesion molecule-1 (VCAM-1) present on the endothelial cells and the CS1 sequence of the fibronectin present in the extracellular matrix.[62] Qureshi et al[63] examined Dupuytren's tissue and the overlying skin histologically for evidence of inflammatory infiltrates. They reported an increased number of S100-positive Langerhans cells (an epidermal cell of dendritic lineage) and CD45-positive cells, both in the nodules and at dermoepidermal junctions, in the biopsied tissues. They proposed that Langerhans cells migrate from the epidermis into Dupuytren's tissue, possibly in response to local changes in the levels of inflammatory cytokines within the tissue. Their findings, together with other reports of increased numbers of dermal dendrocytes and inflammatory cells in Dupuytren's tissue, lend circumstantial support to the 'extrinsic theory' of the pathogenesis of the condition.

Sugden et al[64] have also confirmed the presence of dermal dendrocytes (factor-XIIIa-positive cells) in Dupuytren's tissue. They suggested that this may represent an important link between the skin and the pathogenesis of Dupuytren's disease.

Aetiology of Dupuytren's disease

Dupuytren stated that the condition which now bears his name was firmly associated with local trauma but that not

all cases could be explained in this way.[65] A number of factors have been found to be statistically associated with the development of the disease.

Alcohol. Dupuytren was probably the first to imply an association with alcohol.[66] Although this factor has been recognised for many years[67,68] the role of alcohol has still not been clearly defined. In 1986 in a study of patients admitted for hand surgery Bradlow and Mowat[69] found that Dupuytren's disease among men was strongly associated with heavy drinking. The following year Attali et al[70] reported that the associated variables were, in decreasing order, age, total alcohol consumption, gender (male), and previous hand injuries. In alcoholic patients, the variables were age and previous hand injuries, and in non-alcoholic patients, age and cigarette smoking. They concluded that these results emphasised the high prevalence of the condition in alcoholic patients and the absence of a correlation between it and chronic liver disease.

In another study which compared a group of alcoholics with liver disease (group I) with a group of non-alcoholics with liver disease (group 2) and with control subjects (group 3), Dupuytren's disease was noted in 43% in group 1, 34% in group 2, and in 14% of group 3.[71] In a similar study Noble et al[72] found that the incidence in alcoholics was 28%, in non-alcoholics 22% and in a control group only 8%. Despite the fact that their results did not reach statistical significance, they concluded that alcoholics probably have a higher rate of Dupuytren's disease, largely as a result of liver disease caused by alcohol abuse, but that the genetic factors were of greater aetiological importance.

Smoking. The first association with smoking was identified by Fraser-Moodie in 1976.[73] Since then, several studies have linked microvascular impairment with the condition. An et al[74] concluded from their study of patients compared with a control group, that cigarette smoking is linked statistically to Dupuytren's disease. They suggested that it may be involved in the pathogenesis by producing microvascular occlusion and subsequent fibrosis and contracture or by some other mechanism. Eadington, Patrock and Frier[75] studied patients with type-II diabetes and found that cigarette smoking was positively associated with Dupuytren's disease in the diabetic patients and in the control group. They suggested that type-II diabetes is only one of a number of factors which promote the development of the condition.

In a case-control study in which 222 patients were matched after operation for age, operation date and gender with control patients having other orthopaedic procedures, it was shown that smoking had a strong effect on the risk of developing Dupuytren's disease,[76] with alcohol having a moderate effect. In the Reykjavik Study in Iceland it was found to be common among heavy smokers (p = 0.018).[77]

Manual work. Again, it was Dupuytren who declared that there was an association between his disease and manual labour.[9] Goyrand[78] contested the role of manual work and cited the case of his hospital manager with bilateral disease who had "never put in a day of hard work".[78] Thus began the debate.

The epidemiology of Dupuytren's disease and occupation has been used both to support and to refute an association between manual labour and the condition.[1,79-83] There is a large body of evidence which indicates that there is no significant correlation between occupation and the risk of developing the disease.[1,79,80,84-86] Most studies have shown that manual workers and non-manual workers have an almost equal incidence and that dominant and non-dominant hands are affected equally.[87] Hueston[88] stated that cessation of manual work is often followed by acceleration of the disease process.

The only exception to this is in patients exposed to vibration in the course of their work. The condition has been observed more often among workers exposed to vibration than in control subjects (OR 2.6; 95% CI 1.2-5.5).[89] Cocco et al[90] also found that a history of vibration exposure occurred more often among those affected than among control subjects (OR 2.3; 95% CI 1.5-4.4). These two studies present some evidence of a dose-response relationship which gives good support for an association with vibration exposure.[81]

Injury. In 1968, Hueston[91] described the onset of Dupuytren's disease after a fracture of the distal radius. This was followed by a study by Stewart, Innes and Burke[92] of 235 patients with displaced Colles' fractures who were followed to union; 209 of these were reviewed for six months, specifically for investigation of hand pathology. Sixteen patients developed Dupuytren's disease between three and six months, an incidence of 11%. In another study of the association with trauma Livingston and Field[93] recruited 72 patients with Colles' fractures. They were examined at nine weeks for evidence of algodystrophy and then again 18 months later for evidence of Dupuytren's disease. Forty-one per cent of all patients had evidence of the condition. Sixty-seven per cent of patients with algodystrophy had evidence of Dupuytren's disease compared with 19% of those who showed no features of algodystrophy. Disuse of the hand can also predispose to the development of the disease.[93] Therefore whether algodystrophy or disuse, or both, represent aetiological factors is yet to be determined.

In some Eastern European countries the condition is classified as an industrial disease, whereas in other areas it is considered to have no relation to manual work or hand injury.[94] It is generally accepted that a single injury cannot cause the disease but may precipitate its development in genetically predisposed individuals.[80,94] McFarlane has itemised the following prerequisites for the diagnosis of Dupuytren's disease arising as a result of trauma: 1) first presentation before the age of 40 years in men and 50 in women; 2) in bilateral disease signs in the uninjured hands before the age of 40 years in men and 50 in women; 3) objective evidence of injury of the hand; 4) development must occur at the site of the injury; and 5) appearance within two years of the injury.[95]

Diabetes mellitus. About 5% of people with Dupuytren's disease have diabetes (type I or II).[96] In a study by Noble, Heathcote and Cohen[97] the incidence of the disease in diabetics was 43% and in a control group it was 18% (p = 0.001). The age of onset and the duration of diabetes are significant in type-1 diabetics.[98] After 20 years, 67% of diabetic patients will have Dupuytren's disease.[99] Arkkila et al,[98] in a longitudinal study of 207 young men with type-1 diabetes, found that it developed in 17 patients (2% per year) during the five years of the study. The age of the subjects and the duration of diabetes were the only factors associated with its development. Type-2 diabetics with Dupuytren's disease have a four-fold increased risk of developing macroalbuminuria than those without.[100] In men, an elevated fasting blood sugar has been correlated with the presence of the disease.[77]

Epilepsy/seizure disorders. There is little conclusive evidence to link Dupuyten's disease with seizure disorders. It was found that there was an increased rate of epilepsy of 3% in patients with the disease compared with 1.5% in the general population.[99] The reported incidence in epileptics varies from 12.0% to 56% and increases with increasing age.[101,102] The role of antiepileptic drugs has been raised but there is no confirmatory evidence.[102,103] Frosher and Hoffman[104] reported the regression of cords and knuckle pads after discontinuation of phenobarbitone.

Serum lipids. Sanderson et al[105] studied prospectively the relationship between serum lipids and lesions in the hand in 85 patients, 65 men and 20 women. The Dupuytren's patients had significantly higher fasting serum cholesterol and triglyceride levels than did the control group (p < 0.001). The raised levels of serum lipids may help to explain the high incidence in alcoholic, diabetic and epileptic patients, since these conditions are also associated with raised levels of serum lipid.[105] Caroli et al[106] studied the level of serum triglycerides in Dupuytren's disease since a significant correlation between arcus senilis and hyperlipidaemia had previously been reported.[106] They collected blood samples from each of 336 patients to evaluate the serum level of cholesterol and tryglicerides. The results revealed dyslipidaemia in 54.8% of patients with Dupuytren's disease and in 60.2% of patients who also had arcus senilis. Based on these findings, they suggested that a lipid disorder may be a common aetiopathogenic factor. In particular, they favoured the possible role of hyperlipidaemia.

Rheumatoid disease. There is a statistically significant lower incidence of the condition in patients with rheumatoid arthritis than in age- and gender-matched control subjects.[107] In the Reykjavik study[108] it was suggested that the reason for a negative association with joint complaints was not clear but that genetic and immunological factors may be important. Murrell et al,[48] based on their work with oxygen free radicals, have suggested that the lower prevalence in rheumatoid disease may be due to the administration of large quantities of prostaglandin inhibitors.

Peyronie's disease. In a 1982 case-control study Carrieri et al[109] found that the incidence of Dupuytren's disease in 134 patients with Peyronie's disease was 21% compared with 0% in 134 control subjects with a median age of 58 years. This low incidence in the control group is probably representative of that in southern Europe.[110] A form of autosomal dominant Peyronie's disease with a high incidence of Dupuytren's disease (78%) has been identified.[111]

Genetic factors. Goyrand[78] first described the familial tendency for the transmission of the condition in 1833. The striking variation in prevalence, approaching 30% in individuals over the age of 65 years in Norway, is strong evidence for an inherited susceptibility.[112] It remains unclear whether it is a simple Mendelian disorder or a complex trait like diabetes and heart disease.[110] In many pedigrees, inheritance appears to follow the autosomal dominant model. A family history has been reported by Skoog (22 of 50 cases),[113] Stackebrandt (five of 17 patients),[114] Schroder (10 of 30 cases)[115] and Kozlowski et al (17 of 42 cases).[116] The conclusion is that an autosomal trait operates in some families but not in others.[113,117] A major study was carried out in Edinburgh by Ling[118] who examined the relatives of patients with Dupuytren's disease. He reported that of those aged 60 years or older, 53% of the men and 33% of the women had signs of the disease and provided strong evidence of a genetic influence.[118]

Other modes of inheritance are consistent with the data, however, and it remains unclear whether the many apparently sporadic cases have a genetic basis. The inherited susceptibility may influence the tissue's sensitivity to the effects of environmental exposures. High prevalence, late age of onset, and the possibility of non-genetic cases are features which complicate genetic studies, as can be seen from estimates of relative risk. Identification of susceptibility loci is a worthwhile goal since it may throw new light on the nature of the disease and ultimately open avenues for new treatments.[110]

At present the genetic trait of autosomal dominant with variable penetrance is regarded by some authors as little more than an informed guess. An autosomal recessive trait would account for the mixture of inherited and sporadic cases. For a disease prevalence of 10%, one case in three would have an affected parent and a 50% risk to siblings, whereas two cases in three would have unaffected parents and a 25% risk to siblings. These proportions are similar to those reported for Dupuytren's disease allowing for the uncertainties of late age of onset.[110] An alternative hypothesis is that it is a complex trait similar to ischaemic heart disease, diabetes, hypertension and cancer.

Studies by Bayat et al[119,120] have implicated TGF-β1, suggesting that it may represent a candidate susceptibility gene for this condition. An investigation of the association of nucleotide polymorphisms in TGF-β1 with the risk of developing the condition showed that there was no statistically significant difference in the TGF-β1 genotype or allele frequency distributions between the patients and control

subjects for the codons 10, 25, -509 and -800 polymorphisms. They concluded that common TGF-β1 polymorphisms are not associated with a risk of developing Dupuytren's disease.

Histocompatibility antigens. Some HLA patterns have been identified in the condition but there is no conclusive evidence of this yet. In a study by Spencer and Walsh,[121] 37 consecutive patients were investigated by tissue-typing techniques to ascertain their HLA-A, B, C and DR antigen status. While no definite HLA antigen was found in association with this disease, at least one possibly significant pattern of HLA DR antigens was encountered. This finding was also noted in patients with scleroderma, and the scleroderma-like syndrome induced by exposure to vinyl chloride.

Hormone receptors. Androgen receptors have been studied in Dupuytren's myofibroblasts on the basis that they may have a role in its high male predominance. In a study of hormone levels in patients with the condition, Kuznetsova and Gaev[122] identified a change in tissue sensitivity to the action of androgens. From another study of androgen receptors in Dupuytren's myofibroblasts, Pagnotta, Speechia and Greco[123] presented the first evidence that the palmar fascia is a target tissue for androgen action and that the expression of androgen receptors in the disease is considerably higher than that in the normal palmar fascia.

Hankin, Eckenrode and Louis[124] have examined Dupuytren's tissue for oestrogen and progesterone receptors and found no hormone-specific receptors to be present.

Epidemiology

Most patients with Dupuytren's disease are native to or descendants of ancestors from northern Europe.[125] Many of the large studies on the incidence and prevalence of the condition are Scandinavian, but because it is relatively common among Scandinavians the data cannot necessarily be extrapolated to other populations.

Methods. Because the gathering of longitudinal risk data on the incidence of a disease is difficult, time-consuming and expensive, most epidemiological studies of the condition have assessed prevalence (a snap-shot in time) rather than incidence (the development of the disease in a group over a prolonged period). In some epidemiological studies there is also concern about the accuracy of the diagnosis. Noble et al[97] established a study to assess the accuracy of diagnosis by devising a four-point scheme. They found that the prevalence in the cohort was 18% when examined by a diabetes physician and 42% when examined by a hand surgeon. In another study, by Lennox, Murali and Porter[126] two orthopaedic surgeons, both with experience in the condition, examined a group of patients. Using the Kappa test the agreement between the two observers was found to be, on average, 1.0 for observing flexion contractures, 0.8 for observing skin tethering, 0.7 for observing palmar nodules and 0.7 for observing knuckle pads. The two observers both made the diagnosis in 21% of women and 39% of men.

Prevalence. It has been stated that approximately 4% to 6% of Caucasian populations have evidence of Dupuytren's disease[1,127] and that it is twice as common in men.[128] In a small Norwegian town, Mikkelsen[112] examined 71% of the men and 82% of the women of the total population. He found that the prevalence of the condition was 9.4% in men and 2.8% in women. In another study in Iceland, Gudmundsson et al[77] reported that the prevalence of clinical evidence was 19.2% and 4.4% in women.

Age. Dupuytren himself noted the eponymous contracture in a child aged six years but recorded that it had been present at birth which means that he was probably describing camptodactyly.[96] More recently it has been seen in children as young as nine years.[129] The prevalence of the condition increases with age[77] with men and women being affected with equal frequency after the age of 80 years.[86,96] Men typically present for treatment in the fifth decade and women a decade later.[86,96,112]

Race. Dupuytren's disease has been reported sporadically in non-white races;[130] in particular, in black Americans.[131] Some authors have disputed the purity of racial descent of any such afflicted individuals.[132] It was observed in a Tanzanian tribesman from an isolated tribe which had had no contact with Caucasians before he was born.[133] Zaworski and Mann[134] reported the occurrence of bilateral disease in a black male in Miami, but the family history of no inter-racial marriages was for only two generations. They claimed that this was the sixth reported example, the other five being described by Yost et al[85] and Su and Patek.[135] However, despite numerous other isolated reports of Dupuytren's disease in black patients[136-138] there remains little conclusive evidence of the prevalence in black-skinned races.

The condition has also been reported in Japanese but it has been suggested that it occurs mainly in northern Japan. These people are taller and fairer skinned than those in the south of the country and it is thought that some genetic contamination may have occurred in the times of the long eastward migration of the Uralic-language-speaking peoples.[139,140] The incidence of the disease in the Japanese is similar to that in northern Europe[141,142] although it is much less severe and many do not progress to the stage of contracture of the metacarpophalangeal joints.

Brouet[143] found that the prevalence of blue eyes in 450 patients was 70% but only 40% in 300 control subjects. Similarly, in Piedmont there was a higher prevalence in individuals with straight hair and pale eyes.[144] Vathana, Setpakdi and Srimongkol[145] described nine cases in Thailand and reviewed another ten, the only cases reported in the literature from this country. Other reports from the East and the Orient have been sketchy but include case studies from Taiwan[146] and India and Pakistan.[147]

Conclusion

Dupuytren's disease remains something of an enigma. Many pieces of the jigsaw have been gathered but the entire picture is still far from complete.

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